Remarks

Claims 1-19 are pending in the subject application and Applicants acknowledge that claims 20-30 stand withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicant has cancelled claims 1-19 and added new claims 31-32. Support for the amendments can be found throughout the subject specification. Entry and consideration of the new claims presented herein is respectfully requested. Accordingly, claims 31-32 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Examiner Interview

Applicant thanks Examiner Foster and Examiner Le for the telephonic interview on July 25, 2006.

Claim Objections

The Examiner objected to a number of claims due to informalities. Applicant's new claims render Examiner's objections moot.

Claim Rejections - 35 U.S.C. §112

Claims 1-19 are rejected under 35 U.S.C. §112, second paragraph, as failing to comply with the written description requirement. Examiner argued that "the claims are drawn to a method of making a vaccine composition comprising a protein which is capable of stimulating the production of neutralizing antibodies against a pathogen from which the protein was derived." In addition Examiner argued that "the specification does not disclose any specific structures of conformational variants capable of stimulating the production of neutralizing antibodies that were produced according to the claimed method." Applicant's current claims are claiming a method of producing new conformational variants by altering both the denaturing conditions and the refolding conditions of a target protein. Applicant's current claims use known antibodies to evaluate new conformational variants. The current claims no longer require the conformational variant to stimulate an immune response. Applicant's current claims

comply with the written description requirement. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112 is respectfully requested.

Claim Rejections - 35 U.S.C. §102

Claims 1-10, 12-13, and 15 are rejected under 35 U.S.C. §102(b) as anticipated by Lang et al. ("Monoclonal Antibodies that Define Neutralizing Epitopes of Pertussis Toxin: Conformational Dependence and Epitope Mapping" *Infection and Immunity*, 1989, Vol. 57, p. 2660-2665) in light of Kiernan (Formaldehyde, formalin, paraformaldehyde and glutaraldehyde: What they are and what they do" *Microscopy Today* 00-1 p. 8-12 (2000). The Office Action argues that the Lang reference teaches:

> "a method of producing a composition comprising an protein antigen (pertusis toxin, PT), comprising providing a plurality of samples comprising PT that differ with respect to conformation state of the protein."

Further, the Office action argues that the Kiernan reference:

> "is relied upon as en evidentiary reference for its teaching that formalin, which was reacted with PT by Lang et al., is a covalent linker in that it forms covalent corss-links or methylene bridges between protein atoms."

Applicants respectfully submit that the cited reference fails to anticipate new claims 31 and 32. Applicants submit that Lang does not teach a method of identifying a conformational variant by altering both the denaturing conditions and the refolding conditions to create new conformational variants. Lang only denatures a protein with formalin. Lang does not denature the protein under multiple conditions and does not refold the protein under multiple conditions. Thus, Lang fails to anticipate Applicant's new claims. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

Claims 1, 3-8, 12-13, and 15-16 are rejected under 35 U.S.C. §102(b) as anticipated by Berman et al. (US 6,331,404). The Office Action argues that the Berman reference teaches:

a method of producing a compositions comprising a protein antigen (HIV envelope proteins such as gp120) that are capable of stimulating the production of neutralizing antibodies against HIV (the abstract and column 3, lines 5-37). Berman et al teach providing a plurality of gp120 samples (gp120 fragments, mutagenized gp120 fragments, and/or gp120 proteins isolated from different HIV strains (column 6, lines 43-51; column 9, lines 3-39; column 11, lines 60-67). These samples differ with respect to the conformational state because they have different amino acid sequences.

Applicants respectfully submit that the cited patent fails to anticipate new claims 31 and 32. Applicants submit that Berman does not teach a method of identifying a conformational variant by altering the denaturing conditions and the refolding conditions to create new conformational variants. Berman does not teach altering the conformational state of a protein as claimed by Applicant. Berman attempts to create neutralizing antibodies to gp120 by creating an immune reaction against various fragments of gp120. Thus, Berman alters the amino acid sequence of the protein. Applicant's invention provides a method to alter the conformational state or tertiary structure of a protein with a specific amino acid sequence. Thus, Berman fails to anticipate Applicant's new claims. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

Claim Rejections - 35 U.S.C. §103(a)

Claim 11 is rejected under 35 U.S.C. §103(a) as unpatentable over Lang et al. in light of Kiernan and in view of Densham et al. (US 6,623, 929). Claim 11 states "wherein said linker target is created by in vitro mutagenesis of the amino acid sequence or a nucleic acid sequence encoding said protein." Applicant contends that this rejection is moot in light of the cancellation of claim 11 and the addition of Applicant's new claims 31 and 32. Applicant's are no longer claiming a process which involves mutagenesis to obtain a conformational variant. Applicant's new claims 31 and 32 require the same amino acid sequence among a target protein's different conformational variants. Applicants submit that Lang et al. in light of Kiernan and in view of Densham et al. do

not teach or suggest a method of identifying a conformational variant by altering both the denaturing conditions and the refolding conditions to create new conformational variants. Accordingly, allowance of claims 31 and 32 is respectfully requested.

Claim 14 is rejected under 35 U.S.C. §103(a) as unpatentable over Lang et al. in light of Kiernan and in view of Rasmunssen et al. (US 4,743,562). Claim 11 states "wherein said samples are enriched using one or more neutralizing antibodies." Applicant contends that this rejection is moot in light of the cancellation of claim 14 and the addition of Applicant's new claims 31 and 32. Applicants are no longer claiming a process which enriches samples using neutralizing antibodies. Applicants submit that Lang et al. in light of Kiernan and in view of Rasmunssen et al. do not teach or suggest a method of identifying a conformational variant by altering both the denaturing conditions and the refolding conditions to create new conformational variants. Accordingly, allowance of claims 31 and 32 is respectfully requested.

Claims 17-19 are rejected under 35 U.S.C. §103(a) as unpatentable over Berman et al. or, alternatively, Lang et al. in light of Kiernan, and in view of O'Hagan et al (US 6,458,370). Claim 17 states "wherein said conformational variant is bound to a microparticle having a diameter up to 150um." Claims 18-19 are dependent upon claims 17. Applicant contends that this rejection is moot in light of the cancellation of claims 17-19 and the addition of Applicant's new claims 31 and 32. Applicants are no longer claiming a conformational variant bound to a microparticle. Applicant's new claims 31 and 32 relate to methods of identifying new conformational variants. Applicants submit that Berman et al. or, alternatively, Lang et al. in light of Kiernan, and in view of O'Hagan et al do not teach or suggest a method of identifying a conformational variant by altering both the denaturing conditions and the refolding conditions to create new conformational variants. Accordingly, allowance of claims 31 and 32 is respectfully requested.

Conclusion

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the

Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that currently pending claims 31 and 32 are in condition for allowance, and such action is respectfully requested. Should there be any fees required at this time, the Commissioner is hereby authorized to charge the required fees to Deposit Account No. 502626.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Transform Pharmaceuticals, Inc.
c/o Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933
Telephone: (781) 674-7816
Facsimile: (732) 524-2808

/Paul Burgess/

Paul Burgess, Attorney for Applicants
Reg. No. 53,852
Customer No. 27777